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Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Management of the Treatment-Experienced Patient

Virologic Failure (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations
• Assessing and managing a patient who is experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.
• Evaluation of virologic failure should include an assessment of adherence, drug-drug and drug-food interactions, drug tolerability, HIV RNA level and CD4 T lymphocyte (CD4) cell count trends over time, ART history, and prior and current drug-resistance test results.
• Drug-resistance testing should be performed while the patient is taking the failing antiretroviral (ARV) regimen **(AI)** or within 4 weeks of treatment discontinuation **(AII)**. Even if more than 4 weeks have elapsed since ARV drugs were discontinued, resistance testing can still provide useful information to guide therapy, although it may not detect previously selected resistance mutations **(CIII)**.
• The goal of treatment for ART-experienced patients with drug resistance who are experiencing virologic failure is to establish virologic suppression (i.e., HIV RNA levels below the lower limits of detection of currently used assays) **(AI)**.
• A new regimen should include at least two, and preferably three, fully active agents **(AI)**. A fully active agent is one that is expected to have uncompromised activity based on the patient's ART history and current and past drug-resistance test results. A fully active agent may also have a novel mechanism of action.
• In general, adding a single ARV agent to a virologically failing regimen **is not recommended**, because this may risk the development of resistance to all drugs in the regimen **(BII)**.
• For some highly ART-experienced patients with extensive drug resistance, maximal virologic suppression may not be possible. In this case, ART should be continued **(AI)** with regimens that are designed to minimize toxicity, preserve CD4 counts, and delay clinical progression.
• It is crucial to provide continuous adherence support to all patients before and after regimen changes due to virologic failure.
• Data from an observational study in Botswana suggest that there is an increased risk of neural tube defects (NTDs) in infants born to individuals who were receiving dolutegravir (DTG) at the time of conception; however, the risk of these defects is still low. In patients with virologic failure who are of childbearing potential and who are not using effective contraception or who are contemplating pregnancy, the following factors should be considered:
• Clinicians should review Table 6b for information to consider when choosing to initiate or continue an integrase strand transfer inhibitor.
• If there is an active ARV agent that can be used in place of DTG, DTG should not be prescribed **(AII)**.
• If no alternatives exist, providers and patients should discuss the possible risk of NTDs and weigh that risk against the risks of persistent viremia in the patient and HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART. The decision of whether to initiate or continue DTG should be made after carefully considering these risks.
• When it is not possible to construct a viable suppressive regimen for a patient with multidrug-resistant HIV, the clinician should consider enrolling the patient in a clinical trial of investigational agents or contacting pharmaceutical companies that may have investigational agents available.
• When switching an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.
• Discontinuing or briefly interrupting therapy may lead to a rapid increase in HIV RNA, a decrease in CD4 count, and an increase in the risk of clinical progression. Therefore, this strategy **is not recommended** in the setting of virologic failure **(AI)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Antiretroviral (ARV) regimens that are currently recommended for initial therapy in patients with HIV have a high likelihood of achieving and maintaining plasma HIV RNA levels that are below the lower limits of

detection (LLOD) of currently used assays (see What to Start). Patients on antiretroviral therapy (ART) who do not achieve this treatment goal or who experience virologic rebound can develop resistance mutations to one or more components of their regimen. Adherence to ART regimens can be challenging for some patients, and poor adherence can result in detectable viral loads. Depending on their treatment histories, some of these patients may have minimal or no drug resistance and others may have extensive resistance. Managing patients with extensive resistance is complex and usually requires consultation with an HIV expert. This section of the guidelines defines virologic failure in patients on ART and discusses strategies to manage ART in these individuals.

Virologic Response Definitions

The following definitions are used in this section to describe the different levels of virologic response to ART:

Virologic Suppression: A confirmed HIV RNA level below the LLOD of available assays.

Virologic Failure: The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.

Incomplete Virologic Response: Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in a patient who has not yet had documented virologic suppression on this regimen. A patient's baseline HIV RNA level may affect the time course of response, and some regimens may take longer than others to suppress HIV RNA levels.

Virologic Rebound: Confirmed HIV RNA level ≥200 copies/mL after virologic suppression.

Virologic Blip: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Low-Level Viremia: Confirmed detectable HIV RNA level <200 copies/mL.

Antiretroviral Therapy Treatment Goals and Presence of Viremia While on Antiretroviral Therapy

The goal of ART is to suppress HIV replication to a level below which drug-resistance mutations do not emerge. Although not conclusive, the evidence suggests that selection of drug-resistance mutations does not occur in patients with HIV RNA levels that are persistently suppressed below the LLOD of current assays.[1]

Virologic blips are not usually associated with subsequent virologic failure.[2] In contrast, there is controversy regarding the clinical implications of persistently low HIV RNA levels that are between the LLOD and <200 copies/mL in patients on ART. Viremia at this threshold is detected with some frequency by commonly used real-time polymerase chain reaction (PCR) assays, which are more sensitive than the PCR-based viral load platforms used in the past.[3-5] Findings from a large retrospective analysis showed that, as a threshold for virologic failure, HIV RNA levels of <200 copies/mL and <50 copies/mL had the same predictive value for subsequent rebound as HIV RNA levels of >200 copies/mL.[6] Two other retrospective studies also support the supposition that virologic rebound is more likely to occur in patients with viral loads >200 copies/mL than in those with low-level viremia between 50 copies/mL and 199 copies/mL.[7,8] However, other studies have suggested that detectable viremia at this low level (<200 copies/mL) can be predictive of progressive viral rebound[9,10] and can be associated with the evolution of drug resistance.[11]

Persistent HIV RNA levels ≥200 copies/mL are often associated with evidence of viral evolution and accumulation of drug-resistance mutations.[12] This association is particularly common when HIV RNA levels are >500 copies/mL.[13] Therefore, patients who have persistent plasma HIV RNA levels ≥200 copies/mL are considered to be experiencing virologic failure.

Causes of Virologic Failure

Virologic failure can occur for many reasons. Data from patient cohorts in the earlier era of combination ART suggested that suboptimal adherence and drug intolerance/toxicity are key contributors to virologic failure and regimen discontinuations.[14,15] The presence of pre-existing (transmitted) drug resistance may also lead to virologic failure.[16] Virologic failure may be associated with a variety of factors, including:

Patient/Adherence-Related Factors (see Adherence to the Continuum of Care)

- Comorbidities that may affect adherence (e.g., active substance abuse, mental health disorders, neurocognitive impairment)
- Unstable housing and other psychosocial factors
- Missed clinic appointments
- Interruption of or intermittent access to ART
- Cost and affordability of ARV drugs (i.e., these factors may affect the ability to access or continue therapy)
- Adverse drug effects
- High pill burden and/or dosing frequency

HIV-Related Factors

- Presence of transmitted or acquired drug-resistant virus documented by current or past resistance test results
- Prior treatment failure
- Innate resistance to ARV drugs
- Higher pretreatment HIV RNA level (some regimens may be less effective at higher levels)

Antiretroviral Regimen-Related Factors

- Suboptimal pharmacokinetics (PKs) (e.g., variable absorption, metabolism, or penetration into reservoirs)
- Suboptimal virologic potency
- Low genetic barrier to resistance
- Reduced efficacy due to prior exposure to suboptimal regimens (e.g., monotherapy, dual-nucleoside reverse transcriptase inhibitor (NRTI) therapy, or the sequential introduction of drugs)
- Food requirements
- Adverse drug-drug interactions with concomitant medications
- Prescription errors

Managing Patients with Virologic Failure

If virologic failure is suspected or confirmed, a thorough assessment of whether one or more of the above factors could have been the cause(s) of failure is indicated. Often the causes of virologic failure can be identified, but in some cases, they are not obvious. It is important to distinguish among the causes of virologic failure because the approaches to subsequent therapy may differ depending on the cause. Potential causes of virologic failure should be explored in depth. Once virologic failure is confirmed, steps should be taken to improve virologic outcomes. Those approaches are outlined below.

Key Factors to Consider When Designing a New Antiretroviral Regimen

- Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs, which should be selected after considering the patient's ART history and current and previous resistance test

results and whether an ARV drug with a new mechanistic action is available **(AI)**.[9,17-26]

- Despite the presence of some drug-resistance mutations, some ARV drugs in the regimen may still have partial activity against the patient's HIV and may be retained as part of a salvage regimen. These drugs may include NRTIs or protease inhibitors (PIs).[27] Other agents will likely have to be discontinued, as their continued use may lead to further accumulation of resistance mutations and jeopardize treatment options with newer drugs from the same drug class. These drugs may include enfuvirtide (T-20); non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially efavirenz, nevirapine, and rilpivirine; and the first-generation integrase strand transfer inhibitors (INSTIs) raltegravir (RAL) and elvitegravir (EVG).[28-30]

- Using a drug that a patient has never used previously does not ensure that the drug will be fully active; there is a potential for cross-resistance among drugs from the same class.

- Archived drug-resistance mutations may not be detected by standard drug-resistance tests, particularly if testing is performed when the patient is not taking the drug in question.

- When constructing a salvage regimen, it is more important to consider drug potency and viral susceptibility based on cumulative genotype data than the number of component drugs.

- Resistance testing should be performed while the patient is still taking the failing regimen or within 4 weeks of regimen discontinuation if the patient's plasma HIV RNA level is >1,000 copies/mL **(AI)**, and possibly even if it is between 500 copies/mL and 1,000 copies/mL **(BII)** (see Drug-Resistance Testing). In some patients, resistance testing should still be considered even after treatment interruptions of >4 weeks, though clinicians should recognize that the lack of evidence of resistance in this setting does not exclude the possibility that resistance mutations may be present at low levels **(CIII)**. Drug resistance is cumulative; thus, clinicians should evaluate the extent of drug resistance, taking into account a patient's ART history and, importantly, prior genotypic or phenotypic resistance test results. Some assays only detect resistance to NRTIs, NNRTIs, or PIs; INSTI-resistance testing may need to be ordered separately. INSTI-resistance testing should be ordered in patients who experience virologic failure on an INSTI-based regimen. Additional drug-resistance tests for patients who experience failure on a fusion inhibitor **(AII)** and viral tropism tests for patients who experience failure on a CCR5 antagonist **(BIII)** are also available (see Drug-Resistance Testing).

- Discontinuing or briefly interrupting therapy in a patient with overt or low-level viremia **is not recommended**, as it may lead to a rapid increase in HIV RNA and a decrease in CD4 T lymphocyte (CD4) cell count, and it increases the risk of clinical progression **(AI)**[27,31] (see Discontinuation or Interruption of Antiretroviral Therapy).

- When changing an ARV regimen in a patient with hepatitis B virus (HBV)/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage (see Hepatitis B (HBV)/HIV Coinfection).

The Use of Integrase Strand Transfer Inhibitors in Persons of Childbearing Potential

Because the use of INSTIs is frequently considered for persons who are experiencing virologic failure, clinicians should be aware that preliminary data from Botswana suggest that there is an increased risk of neural tube defects (NTDs) in infants born to individuals who were receiving dolutegravir (DTG) at the time of conception (0.9%).[32,33] Follow-up data showed that the prevalence of NTDs in infants who were exposed to DTG is lower than reported in the preliminary data (0.3%), but still higher than in infants born to women who received ART that did not include DTG (0.1%).[34,35] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review the information in Table 6b.

When DTG is the only treatment option (or one of few treatment options) for persons of childbearing potential with virologic failure, providers and patients should discuss the possible risk of NTDs and weigh

that risk against the risks of persistent viremia in the patient and HIV transmission to the fetus if pregnancy occurs while the patient is not on effective ART. The decision of whether to initiate or continue DTG should be made after carefully considering these risks.

Clinicians should note that there are insufficient safety data on the use of bictegravir (BIC) around the time of conception and during pregnancy to guide evidence-based recommendations. An approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**.

Antiretroviral Drug Strategies

- In general, patients who receive at least three active drugs experience better and more sustained virologic response than those who receive fewer active drugs. These three drugs should be selected based on the patient's ART history and a review of their drug-resistance test results, both past and present.[18,19,21,22,36-38]

- Active drugs are ARV drugs that, based on current and previous resistance test results and ART history, are expected to have antiviral activity equivalent to the activity seen when there is no resistance to the specific drugs. ARV drugs with partial activity are those predicted to reduce HIV RNA, but to a lesser extent than when there is no underlying drug resistance.

- Active drugs may be newer members of existing drug classes that are active against HIV isolates that are resistant to older drugs in the same classes (e.g., etravirine, darunavir [DRV], and DTG).

- An active drug may also be one with a mechanism of action that is different from the mechanisms of the ARV drugs that were previously used in that individual (e.g., the fusion inhibitor T-20, the CCR5 antagonist maraviroc in patients with no detectable CXCR4-using virus, and some investigational ARV drugs).

- An increasing number of studies in ART-naive and ART-experienced patients have shown that an active, PK-enhanced PI plus one other active drug or several partially active drugs will effectively reduce viral load in most patients.[39-42]

- In the presence of certain resistance mutations, some ARV drugs, such as DTG, darunavir/ritonavir (DRV/r), and lopinavir/ritonavir (LPV/r), need to be given twice daily instead of once daily to achieve the higher drug concentrations necessary to be active against a less-sensitive virus.[43,44]

Addressing Patients with Different Levels of Viremia

Patients with detectable viral loads comprise a heterogenous group of individuals with different ART exposure histories, degrees of drug resistance, durations of virologic failure, and levels of plasma viremia. Management strategies should be individualized. The first steps for all patients with detectable viral loads are to confirm the level of HIV viremia and assess and address adherence and potential drug-drug interactions (including interactions with over-the-counter products and supplements) and drug-food interactions. Some general approaches based on level of viremia are addressed below.

- **HIV RNA Above the LLOD and <200 copies/mL:** Patients who have these HIV RNA levels do not typically require a change in treatment **(AII)**.[4] Although there is no consensus on how to manage these patients, the risk that resistance will emerge is believed to be relatively low. Therefore, these patients should continue their current regimens and have HIV RNA levels monitored at least every 3 months to assess the need for changes to ART in the future **(AIII)**.

- **HIV RNA Levels ≥200 copies/mL and <1,000 copies/mL:** In contrast to patients with detectable HIV RNA levels that are persistently <200 copies/mL, those with levels that are persistently ≥200 copies/mL often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL.[7,8] Patients who have persistent plasma HIV RNA levels in the range of 200 copies/mL to 1,000 copies/mL are considered to be experiencing virologic failure, and resistance testing should be attempted, particularly in patients with HIV RNA levels >500 copies/mL. Management approaches should be the same as for patients with HIV RNA >1,000 copies/mL (as outlined below). When resistance testing cannot be performed because of low HIV

RNA levels, the decision of whether to empirically change ARV drugs should be made on a case-by-case basis, taking into account whether a new regimen that is expected to fully suppress viremia can be constructed.

- **HIV RNA ≥1,000 copies/mL and No Drug Resistance Mutations Identified Using Current or Previous Genotypic Resistance Test Results:** This scenario is almost always associated with suboptimal adherence. Conduct a thorough assessment to determine the level of adherence, identify and address the underlying cause(s) for incomplete adherence and, if possible, simplify the regimen (e.g., decrease pill count, simplify food requirement or dosing frequency; see Adherence to the Continuum of Care). Approaches include:
    - Assessing the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can affect adherence.
    - Addressing intolerance by treating symptoms (e.g., with antiemetics or antidiarrheals), switching one ARV agent in a regimen to another agent in the same drug class, or switching from one drug class to another class (e.g., from a NNRTI to a PI or an INSTI; see Adverse Effects of Antiretroviral Agents).
    - Reviewing food requirements for each medication and assessing whether the patient adheres to the requirements.
    - Assessing whether there is a recent history of gastrointestinal symptoms (e.g., vomiting, diarrhea) that may result in short-term malabsorption.
    - Reviewing concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult Drug-Drug Interactions and Tables 21a through 22b for common interactions) and, if possible, making appropriate substitutions for ARV agents and/or concomitant medications.
    - Considering therapeutic drug monitoring if PK drug-drug interactions or impaired drug absorption leading to decreased ARV drug exposure is suspected.
    - Considering the timing of the drug-resistance test (e.g., was the patient mostly or completely ART-nonadherent for >4 weeks before testing?).
        - If the current regimen is well tolerated and there are no significant drug-drug or drug-food interactions, it is reasonable to continue the same regimen.
        - If the agents are poorly tolerated or there are important drug-drug or drug-food interactions, consider changing the regimen to an equally effective but more tolerable regimen.
        - Repeat viral load testing 2 to 4 weeks after treatment is resumed or started; if viral load remains >500 copies/mL, perform genotypic testing to determine whether a resistant viral strain has emerged **(CIII)**.
- **HIV RNA >1,000 copies/mL and Drug Resistance Identified:** If new or previously detected resistance mutations compromise the regimen, the regimen should be modified as soon as possible in order to avoid progressive accumulation of resistance mutations.[45] In addition, several studies have shown that virologic responses to new and active regimens are greater in individuals with lower HIV RNA levels and/or higher CD4 counts at the time of regimen changes; thus, the change is best done before viremia worsens or CD4 count declines.[9,46] The availability of newer ARV drugs, including some with new mechanisms of action, makes it possible to suppress HIV RNA levels to below the LLOD in most of these patients. The options in this setting depend on the extent of drug resistance and are addressed in the clinical scenarios outlined below.

Managing Virologic Failure in Different Clinical Scenarios

See Table 11 for a summary of these recommendations.

Virologic Failure with First Antiretroviral Regimen

- **NNRTI plus NRTI Regimen Failure:** These patients often have viral resistance to the NNRTI, with or without the M184V/I mutation, which confers high-level resistance to lamivudine (3TC) and emtricitabine (FTC). Additional NRTI mutations may also be present. Below are some switch options.

  - **Boosted PI plus Two NRTIs:** Three large randomized controlled trials (primarily conducted in resource-limited settings where NNRTI-based regimens have been used as first-line therapy) have explored different second-line regimen options. The studies found that regimens that contained LPV/r plus two NRTIs were as effective as regimens that contained LPV/r plus RAL.[41,42,47] Even though LPV/r was the PI used in these studies, it is likely that other boosted PIs (i.e., DRV/r or atazanavir/ritonavir) would have similar activities and may be tolerated better, although this has not been demonstrated in large clinical trials. The EARNEST study randomized participants to receive LPV/r plus two or three investigator-selected NRTIs, LPV/r plus RAL, or LPV alone. Participants did not undergo resistance testing before randomization.[42] Lower rates of virologic suppression were seen in participants who received LPV/r monotherapy, confirming that ritonavir-boosted PI (PI/r) monotherapy **cannot be recommended (AI)**.[42,48] The virologic responses were similar in the LPV/r plus NRTIs arm and the LPV/r plus RAL arm. A post-hoc analysis showed that viral suppression was achieved in over 80% of the participants who received either no active NRTIs or one active NRTI in their new regimens.[49] It should be noted that most of the participants received thymidine analogs (stavudine or zidovudine—NRTIs that are no longer used in first-line regimens in the United States) plus 3TC. The authors of this trial suggest that, as a public health approach, resistance testing after first-line failure may not be necessary in resource-limited countries. However, in settings where genotypic resistance tests are available, the Panel on Antiretroviral Guidelines for Adults and Adolescents recommends using a boosted PI plus two NRTIs (at least one of which is active) in a regimen **(AIII)**.

  - **DTG plus One or Two Active NRTIs:** In the DAWNING trial, patients who experienced virologic failure while on a first-line, NNRTI-based regimen were randomized to receive either LPV/r or DTG; each of these drugs was given with two NRTIs, one of which had to be fully active based on real-time resistance testing. The study was stopped early after an interim analysis showed that the DTG arm was superior to the LPV/r arm.[50] Thus, DTG plus two NRTIs (at least one of which is active) can be an option after failure of a first-line, NNRTI-based therapy **(AI)**. BIC may have activity that is similar to that of DTG; however, there are currently no data to support its use. There are not enough data on the efficacy of EVG or RAL to recommend the use of these INSTIs in the setting of first-line, NNRTI-based therapy failure.

  - **Boosted PI plus an INSTI:** As noted earlier, a regimen that consisted of LPV/r plus RAL was found to be as effective as LPV/r plus two NRTIs.[41,42,47] Thus, LPV/r plus RAL can also be a treatment option for those who experienced virologic failure on an NNRTI-based regimen **(AI)**. Although data are limited, DTG combined with a boosted PI may also be an option in this setting **(AIII)**. There are no data on the efficacy of BIC or EVG with boosted PI in the setting of first-line, NNRTI-based therapy failure.

- **Boosted PI plus NRTI Regimen Failure:** In this scenario, most patients will have either no resistance or resistance that is limited to 3TC and FTC.[51,52] Failure in this setting is often attributed to poor adherence, drug-drug interactions, or drug-food interactions. Below are some management options.

  - **Maintain on the Same Regimen:** A systematic review of multiple randomized trials that investigated the failures of first-line, PI/r-based regimens showed that maintaining the same regimen while making efforts to enhance adherence is as effective as changing to new regimens with or without drugs from new classes **(AII)**.[53] If the regimen is well tolerated and there are no concerns about drug-drug or drug-food interactions or drug resistance, then the regimen can be continued with

adherence support and viral monitoring.

- **Switch to Another Regimen:** If poor tolerability, drug interactions, or drug resistance may be contributing to virologic failure, then the regimen can be modified to:
  - A different boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
  - A different boosted PI plus an INSTI **(BIII)**; *or*
  - An INSTI plus two NRTIs (at least one of which is active) **(AIII)**. As noted above, if only one of the NRTIs is fully active or if adherence is a concern, DTG is the recommended INSTI **(AIII)**. Before considering the use of DTG in persons who are pregnant or who are of childbearing potential, please refer to the earlier discussion regarding the use of DTG and the potential risk of NTDs in infants. There are limited to no data on the efficacy of BIC or EVG in this setting.

- **INSTI plus NRTI Regimen Failure:** Virologic failure in patients on a regimen that consists of RAL or EVG plus two NRTIs may be associated with emergent resistance to 3TC or FTC and possibly the INSTI.[54] Viruses with EVG or RAL resistance often remain susceptible to DTG.[46] In contrast, in clinical trials, persons who experienced virologic failure while receiving BIC or DTG plus two NRTIs as first-line therapy were unlikely to develop phenotypic resistance to BIC or DTG.[54-56] There are no clinical trial data to guide therapy for first-line INSTI failures; therefore, treatment strategy should be based on resistance test results and the potential potency of the next regimen. Below are some treatment options, based on resistance pattern considerations.

  - **Virologic Failure without Any Resistance Mutations:** The patient should be managed as outlined above in the section on virologic failure without resistance.

  - **Virologic Failure without INSTI Resistance:** The regimen can be modified to
    - A boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - A boosted PI plus an INSTI **(AIII)**; *or*
    - DTG plus two NRTIs (at least one of which is active) **(AIII)**.

  - **Virologic Failure with Resistance to RAL and EVG but Susceptibility to DTG:** The regimen can be modified to:
    - A boosted PI plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - Twice-daily DTG plus two NRTIs (at least one of which is active) **(AIII)**; *or*
    - Twice-daily DTG plus a boosted PI **(AIII)**.

There are currently no data on the efficacy of BIC in patients who experience virologic failure while on an EVG- or RAL-based regimen; therefore, this drug cannot be recommended in this setting.

Second-Line Regimen Failure and Beyond

Drug Resistance with Fully Active Antiretroviral Therapy Options

Using a patient's treatment history and drug-resistance data, a clinician can decide whether to include a fully active, boosted PI in future regimens. For example, those who have no documented PI resistance and who have previously never been treated with an unboosted PI likely harbor virus that is fully susceptible to PIs. In this setting, viral suppression should be achievable using a boosted PI combined with either two NRTIs or an INSTI—provided the virus is susceptible to these drugs. If a fully active, boosted PI is not an option, the new regimen should include at least two, and preferably three, fully active agents. Drugs should be selected based on the likelihood that they will be active, as determined by the patient's treatment history, past and present drug-resistance testing, and tropism testing if a CCR5 antagonist is being considered.

Multidrug Resistance without Fully Active Antiretroviral Therapy Options
Use of currently available ARV drugs has resulted in a dramatic decline in the number of patients who have few treatment options because of multiclass drug resistance.[57,58] Despite this progress, there remain patients who have experienced toxicities with and/or developed resistance to all or most currently available drugs. If maximal virologic suppression cannot be achieved, the goals of ART will be to preserve immunologic function, prevent clinical progression, and minimize the development of further resistance that may compromise future regimens.

Consensus on the optimal management of these patients is lacking. If resistance to NNRTIs, T-20, DTG, EVG, or RAL are identified, there is rarely a reason to continue using these drugs, as there is little evidence that keeping them in the regimen helps delay disease progression **(BII)**. Moreover, continuing these drugs (in particular INSTIs) may allow for selection of additional resistance mutations and development of within-class cross resistance that may limit future treatment options. It should be noted that even partial virologic suppression of HIV RNA to >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefit.[57,59] Cohort studies provide evidence that continuing therapy, even in the presence of viremia and the absence of CD4 count increases, reduces the risk of disease progression.[60] Other cohort studies suggest that even modest reductions in HIV RNA levels continue to confer immunologic and clinical benefits.[61,62] However, these potential benefits must be balanced with the ongoing risk of accumulating additional resistance mutations. In general, adding a single fully active ARV drug to the regimen **is not recommended** because of the risk of rapid development of resistance **(BII)**.

Patients with ongoing detectable viremia who lack sufficient treatment options to construct a fully suppressive regimen may be candidates for the recently approved CD4 post-attachment inhibitor ibalizumab (IBA).[63] A single-arm, multicenter clinical trial enrolled 40 heavily ART-experienced participants who had multidrug-resistant HIV and who were experiencing virologic failure on an ARV regimen. Subjects received intravenous infusions of IBA every 2 weeks in addition to an optimized background regimen that included at least one additional agent to which the subject's virus was susceptible. At Week 24, 43% of participants achieved HIV RNA <50 copies/mL, and 50% of participants achieved HIV RNA <200 copies/mL.[64] Of the 27 participants who continued on to the 48-week follow-up study, 59% and 63% had HIV RNA <50 copies/mL and <200 copies/mL, respectively. All 15 patients who had HIV RNA <50 copies/mL at Week 24 maintained viral suppression up to Week 48.[65]

Patients who continue to have detectable viremia and who lack sufficient treatment options to construct a fully suppressive regimen may also be candidates for research studies or expanded access programs, or they may qualify for single-patient access to an investigational new drug as specified in Food and Drug Administration regulations. Information about agents that are in late-stage clinical studies (e.g., fostemsavir, PRO-140), can be found in the drug fact sheets available on AIDS*info*'s website.

Antiretroviral Therapy-Experienced Patients with Suspected Drug Resistance Who Present with Limited Information (Incomplete or No Self-Reported History, Medical Records, or Resistance Test Results)
Every effort should be made to obtain the patient's ARV history and prior drug-resistance test results; however, this may not always be possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2 to 4 weeks to guide the selection of the next regimen. Another strategy is to start two or three drugs that are predicted to be active based on the patient's treatment history. If no ARV history is available, a clinician may consider using agents with a high barrier to resistance, such as twice-daily DTG and/or boosted DRV, as part of the regimen. Before considering the use of DTG in persons who are pregnant or who are of childbearing potential, please refer to the earlier discussion regarding the use of DTG and the potential risk of NTDs in infants. HIV RNA and resistance testing should be obtained approximately 2 to 4 weeks after re-initiation of therapy, and patients should be closely monitored for virologic responses. Lastly, since there are no safety data on the use of BIC around the time of conception to guide evidence-based recommendations, an approach similar to that outlined for DTG may be implemented before considering the use of BIC-containing ART in those of childbearing potential.

Table 11. Antiretroviral Options for Patients with Virologic Failure

Designing a new regimen for patients who are experiencing treatment failure should always be guided by ARV history and results from current and past resistance testing. This table summarizes the text above and displays the most common or likely clinical scenarios seen in patients with virologic failure. For more detailed descriptions, please refer to the text above and/or consult an expert in drug resistance to assist in the design of a new regimen. It is also crucial to provide continuous adherence support to all patients before and after regimen changes.

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
First Regimen Failure	NNRTI plus two NRTIs	Most likely resistant to NNRTI +/- 3TC or FTC (i.e., NNRTI mutations +/- M184V/I).[c] Additional NRTI mutations may also be present.	Boosted PI plus two NRTIs (at least one active) **(AIII)**; *or* DTG[d] plus two NRTIs (at least one active) **(AI)**; *or* Boosted PI plus INSTI **(AIII)**	Resuppression
	Boosted PI plus two NRTIs	Most likely no resistance, or resistance only to 3TC or FTC (i.e., M184V/I, without resistance to other NRTIs)[c]	Continue same regimen **(AII)**; *or* Another boosted PI plus two NRTIs (at least one active) **(AII)**; *or* INSTI plus two NRTIs (at least one active; if only one of the NRTIs is fully active, or if adherence is a concern, DTG[d] is preferred over other INSTIs) **(AIII)**; *or* Another boosted PI plus INSTI **(BIII)**	Resuppression
	INSTI plus two NRTIs	No INSTI resistance (can have 3TC or FTC resistance, i.e., only M184V/I, usually without resistance to other NRTIs)[c]	Boosted PI plus two NRTIs (at least one active) **(AIII)**; *or* DTG[d] plus two NRTIs (at least one active) **(AIII)**; *or* Boosted PI plus INSTI **(BIII)**	Resuppression
		EVG or RAL +/- 3TC or FTC resistance Resistance to first-line BIC or DTG is rare.	Boosted PI plus two NRTIs (at least one active) **(AIII)**; *or* DTG[d,e] twice daily (if HIV is sensitive to DTG) plus two active NRTIs **(AIII)**; *or* DTG[d,e] twice daily (if HIV is sensitive to DTG) plus a boosted PI **(AIII)** BIC has not been studied in this setting and **cannot be recommended**.	Resuppression
Second Regimen Failure and Beyond	Drug resistance with active treatment options	Use past and current genotypic +/- phenotypic resistance testing and ART history when designing new regimen.	At least two, and preferably three, fully active agents **(AI)** Partially active drugs may be used when no other options are available. Consider using an ARV drug with a different mechanism of action.	Resuppression

Table 11. Antiretroviral Options for Patients with Virologic Failure, continued

Clinical Scenario	Type of Failing Regimen	Resistance Considerations	New Regimen Options[a,b]	Goal
Second Regimen Failure and Beyond, continued	Multiple or extensive drug resistance with few treatment options	Use past and current genotypic and phenotypic resistance testing to guide therapy. Consider viral tropism assay when use of MVC is considered. Consult an expert in drug resistance, if needed.	Identify as many active or partially active drugs as possible based on resistance test results. Consider using an ARV drug with a different mechanism of action. Consider enrollment into clinical trials or expanded access programs for investigational agents, if available. Discontinuation of ARV drugs **is not recommended**.	Resuppression, if possible; otherwise, keeping viral load as low as possible and CD4 count as high as possible.
ART-Experienced Patients with Suspected Drug Resistance and Limited or Incomplete ARV and Resistance History	Unknown	Obtain medical records, if possible. Resistance testing may be helpful in identifying drug resistance mutations, even if the patient has been off ART. Keep in mind that resistance mutations may not be detected in the absence of drug pressure.	Consider restarting the old regimen, and obtain viral load and resistance testing 2–4 weeks after reintroduction of therapy. If no ARV history is available, consider initiating a regimen with drugs with high genetic barriers to resistance (e.g., DTG[d,e] and/or boosted DRV).	Resuppression

[a] There are insufficient data to provide a recommendation for the continuation of 3TC or FTC in the presence of M184V/I.

[b] When switching an ARV regimen in a patient with HBV/HIV coinfection, ARV drugs that are active against HBV should be continued as part of the new regimen. Discontinuation of these drugs may lead to the reactivation of HBV, which may result in serious hepatocellular damage.

[c] If other NRTI resistance mutations are present, use resistance test results to guide NRTI usage in the new regimen.

[d] Data from an observational study in Botswana suggest that there is an increased risk of NTDs in infants born to individuals who were receiving DTG at the time of conception; however, the risk of these defects is still low. Please refer to the discussion in the text and in Table 6b before prescribing DTG in persons of childbearing potential.

[e] Response to DTG depends on the type and number of INSTI mutations.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; CD4 = CD4 T lymphocyte; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; RAL = raltegravir

Isolated Central Nervous System Virologic Failure and Neurologic Symptoms

Presentation with new-onset central nervous system (CNS) signs and symptoms has been reported as a rare form of "compartmentalized" virologic failure. These patients present with new, usually subacute, neurological symptoms that are associated with breakthrough of HIV infection within the CNS compartment despite plasma HIV RNA suppression.[66-68] Clinical evaluation frequently shows abnormalities on magnetic resonance imaging and abnormal cerebrospinal fluid (CSF) findings with characteristic lymphocytic pleocytosis.[69] Measurement of CSF HIV RNA shows higher concentrations in the CSF than in plasma, and in most (though not all) patients, there is evidence of drug-resistant CSF virus. Drug-resistance testing of HIV in CSF can be used to guide changes in the treatment regimen according to the principles outlined above for plasma HIV RNA resistance **(CIII)**. In these patients, it may also be useful to consider CNS PKs during drug selection to assure adequate concentrations of drugs within the CNS **(CIII)**. If CSF HIV resistance testing is not available, the regimen may be changed based on the patient's treatment history or on predicted drug penetration into the CNS **(CIII)**.[70-73]

This "neurosymptomatic" CNS viral escape should be distinguished from:

- The incidental detection of asymptomatic and mild CSF HIV RNA elevation, which is similar to plasma blips in that it is usually transient with low levels of CSF HIV RNA;[74,75] *or*

- A transient increase in CSF HIV RNA that is related to other CNS infections that can induce a brief increase in CSF HIV RNA (e.g., herpes zoster).[76]

There does not appear to be an association between these asymptomatic CSF HIV RNA elevations and the relatively common chronic, usually mild, neurocognitive impairment in patients with HIV who show no evidence of CNS viral breakthrough.[77] Unlike the "neurosymptomatic" CNS viral escape, these latter conditions do not currently warrant a change in ART.[78]

Summary

The management of ART-experienced patients with virologic failure often requires expert advice to construct virologically suppressive regimens. Before modifying a regimen, it is critical to carefully evaluate the potential cause(s) of virologic failure, including incomplete adherence, poor tolerability, and drug-drug and drug-food interactions, as well as review HIV RNA and CD4 count changes over time, complete treatment history, and current and previous drug-resistance test results. If HIV RNA suppression is not possible with currently approved agents, consider the use of investigational agents through participation in clinical trials or expanded/single-patient access programs. If virologic suppression is still not achievable, the choice of regimens should focus on minimizing toxicity and preserving treatment options while maintaining CD4 counts to delay clinical progression.

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